SWISS CONFEDERATION
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Int. Cl: C 07 C 93/02
C 07 C 149/14

SWISS PATENT 593 911

Petition No.: 10197/72
Addition to: 575 375
Partial petition of:
Date of application: July 7, 1972, 5:00 p.m.
Priority:

Patent granted on: August 31, 1977
Patent published on: December 30, 1977

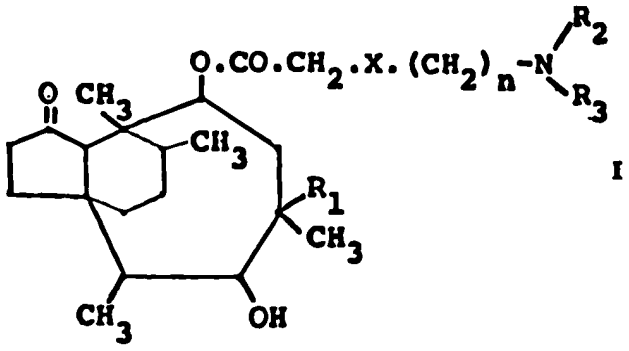
Title: Method for producing new pleuromutiline derivatives

Holder: Sandoz AG, Basel

Represented by:

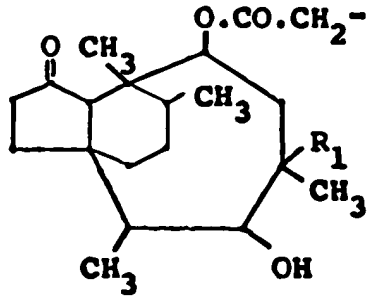
Inventors: Dr. Helmut Egger, Vienna (Austria) and Dr. Hellmuth Reinshagen, Hartheim-Feldkirch (Federal German Republic)

The invention concerns a method for producing new pleuromutiline derivatives of formula I



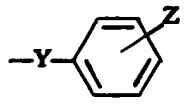
I

In which R_1 stands for the ethyl or vinyl group, n stands for a whole number from 2 through 5, and X stands for sulfur, the group >N-R_4, wherein R_4 means hydrogen or a grouping of formula II



II

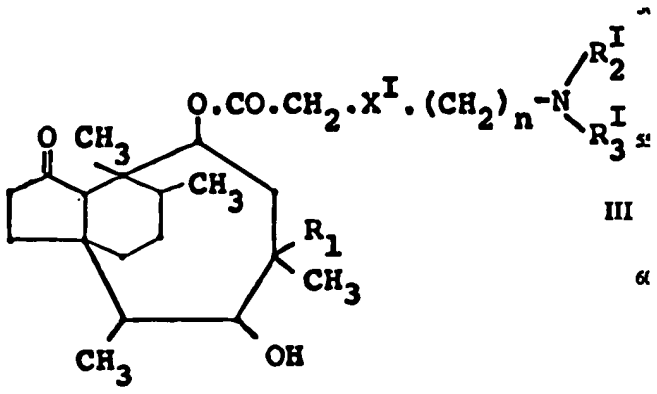
In which R_1 has the meaning above, or a



group

in which, if Y and Z are the same, both stand for sulfur or, if Y and Z are different, they mean sulfur or oxygen, and R_2 and R_3, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5 group wherein R_5 stands for a lower benzoyloxyalkyl group, or wherein, if X stands for >N-R_4 and n stands for 2, R_2 and R_4, jointly with the two nitrogen atoms, form a piperazinyl radical wherein R_3 stands for a lower benzoyloxyalkyl group and their acid addition salts.

The method is characterized in that compounds of formula III



III

In which R_1, X and n have the meaning above and R_2^I and R_3^I, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5^I group wherein R_5^I stands for a lower hydroxyalkyl group or wherein, if X stands for >N-R_4 and n stands for 2, R_2^I and R_4 jointly with the two nitrogen atoms form a piperazinyl radical wherein R_3^I stands for a lower hydroxyalkyl group, are reacted with a compound of formula IV

$$A\text{-}R_5 \qquad \text{IV}$$

wherein A stands for an alkoxycarbonyl, haloformyl or $R_5CO{\bullet}O{\bullet}CO$ group and R_5 stands for the phenyl group, and the compounds of formula I obtained are converted as desired into their acid addition salts.

The starting products are described in the original patent 575 375. Furthermore, the compounds of formula I have the same pharmacological properties as the compounds of formula I described in original patent 575 375 and can therefore be used in the same way.

The tertiary amino compounds of formula I obtained can be quaternated by reaction with a quaternation agent.

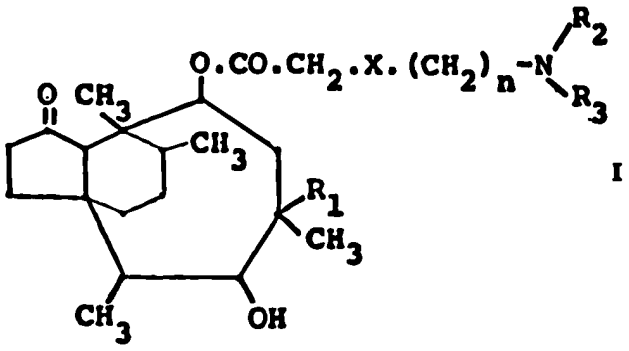
Example

14-deoxy-14-{[2-(4-benzoyloxyethyl)-piperazino]-ethylmercaptoacetoxy} mutiline

0.50 g of 14-{deoxy-14-[2-(4-hydroxyethyl)piperazino]-ethylmercaptoacetoxy} mutiline are boiled with reflux for 2 hours in 5 ml dichloromethane with 0.16 g benzoyl chloride. After cooling, the dihydrochloride is precipitated by the addition of ethereal hydrochloric acid and dilution with absolute ether. Softening point: 132-135°C.

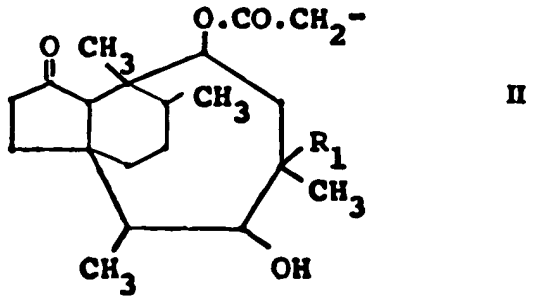
CLAIMS

I. Method for producing compounds of formula I



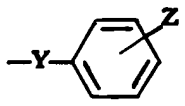
I

In which R_1 stands for the ethyl or vinyl group, n stands for a whole number from 2 through 5, and X stands for sulfur, the group >N-R_4, wherein R_4 means hydrogen or a grouping of formula II



II

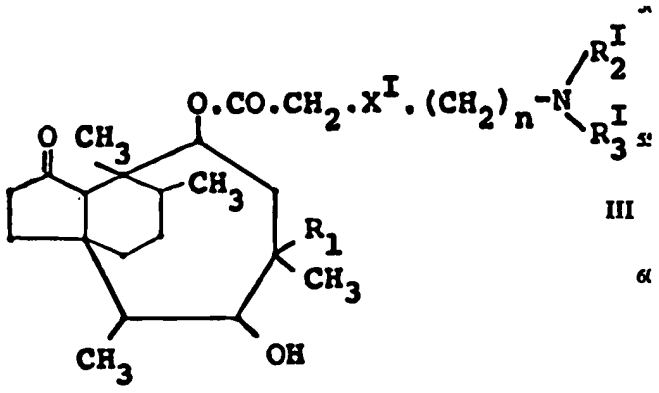
In which R_1 has the meaning above, or a



group

in which, if Y and Z are the same, both stand for sulfur or, if Y and Z are different, they mean sulfur or oxygen, and R_2 and R_3, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5 group wherein
R_5 stands for a lower benzoyloxyalkyl group, or wherein, if X stands for >N-R_4 and n stands for 2, R_2 and R_4, jointly with the two nitrogen atoms, form a piperazinyl radical wherein R_3 stands for a lower benzoyloxyalkyl group and their acid addition salts,

characterized in that compounds of formula III



III

In which R_1, X and n have the meaning above and R_2^I and R_3^I, jointly with the nitrogen atom, form a piperazinyl radical whose second nitrogen atom is substituted by an R_5^I group wherein R_5^I stands for a lower hydroxyalkyl group or wherein, if X stands for >N-R_4 and n stands for 2, R_2^I and R_4, jointly with the two nitrogen atoms, form a piperazinyl radical wherein R_3^I stands for a lower hydroxyalkyl group, are reacted with a compound of formula IV

$$A\text{-}R_5 \qquad \text{IV}$$

wherein A stands for an alkoxycarbonyl, haloformyl or $R_5CO{\bullet}O{\bullet}CO$ group and R_5 stands for the phenyl group, and the compounds of formula I obtained are converted as desired into their acid addition salts.

II. Use of the pleuromutilines of formula I obtained with the method according to claim I for producing their quaternated salts, characterized in that tertiary amino compounds obtained are quaternated with a quaternation agent.

Note by the Swiss Office for Intellectual Property

If parts of the description do not agree with the definition of the invention given in the claims, bear in mind that, under Article 51 of the Patent Law, the claims determine the actual area of validity of the patent.